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09/30/99 JC990 U.S. PTO

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a **PROVISIONAL APPLICATION FOR PATENT** under 37 CFR 1.53 (b)(2).

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TITLE OF INVENTION

TRACELESS LINKING OF INDOLES

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ENCLOSED APPLICATION PARTS

X	Specification: Number of Pages 7		Claims: Number of Pages 0		Small Entity Statement
X	Drawings: Number of Pages 5		Abstract: Number of Pages 0		Other: No. of Pages

METHOD OF PAYMENT

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Respectfully submitted,

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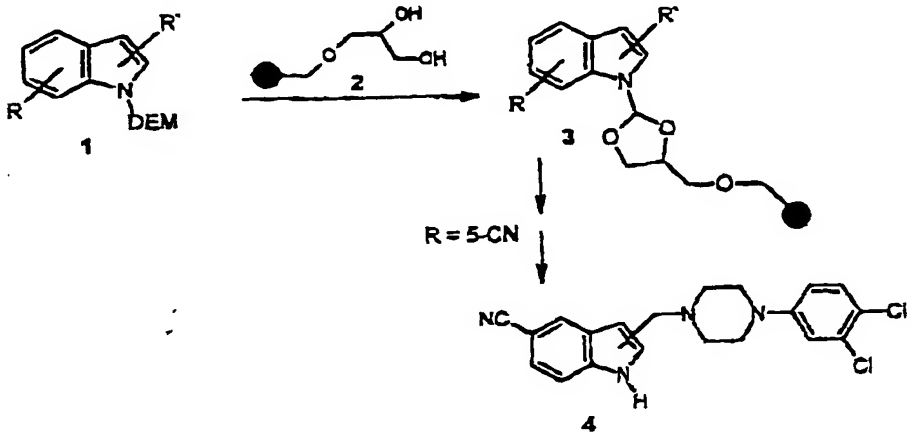
TRACELESS SOLID PHASE METHODOLOGY FOR THE SYNTHESIS OF SELECTIVE DOPAMINE D4 RECEPTOR LIGANDS

A novel traceless linking strategy for indoles has been developed and applied for the synthesis of selective dopamine D4 receptor ligands. Efficient resin attachment of N-diethoxymethyl protected indoles[1] 1 to the glycerol resin 2 could be achieved under mild acidic conditions. Resin-bound indoles 3 were subjected to nucleophilic substitution and Mannich reactions providing the 2- and 3-substituted D4 receptor ligands of type 4 in good yields and excellent purity.



Lit.
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1

Traceless Linking of Indoles: General Methodology and Application to Solid Phase Supported *Mannich* and *Stille* Reactions

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Abstract: Transacetalization reaction of the diethoxymethyl (DEM) protected indoles **2a,b,d,e** with the polymer bound glycerol derivative **3** resulted in formation of the immobilized indoles **4a,b,d,e**. Selective indole-functionalizations and quantitative and traceless cleavage could be demonstrated.

Combinatorial organic synthesis on solid support has emerged as an important tool in lead structure identification and optimization in drug discovery.[1] Within this field, considerable efforts have been made to establish strategies for the synthesis and derivatization of immobilized indoles [2] since the indole nucleus is frequently found as a key structural element in a wide variety of biologically active compounds.[3] A limitation of many solid phase supported methods is that a functional group such as a carboxylic acid or amide remains in the product after the cleavage process. As a consequence, traceless solid phase linkers are currently developed.[4] A first example was also described for indoles.[5]
Recently, we have reported on the use of the diethoxymethyl (DEM) group for the nitrogen protection of lactams, amides [6] and indoles.[7] Due to the stability towards various reaction conditions and its utility to act as a directing metallation group the application of DEM turned out as an advantageous synthetic tool. As a consequence, we were intrigued by the question whether an immobilized dialkoxymethyl derived structural framework utilizing the indole *NH* as a resin attachment point could lead to an effective traceless linking of indoles. In this communication, we describe the first results of our study towards immobilization of DEM protected indoles by transacetalization using polymer-bound 3-

benzyloxypropane-1,2-diol (3) [8] as well as an application for solid phase supported *Mannich* and *Stille* reactions.

The DEM protected representatives **2a-d** were prepared directly from the indoles **1-d** by heating in neat triethyl orthoformate. As a further building block, the stannane **2e** should be elaborated which could be readily synthesized from **2d** in 92 % yield by regioselective lithiation in position 2 and subsequent treatment with tri-n-butyltin chloride.

eq 1

Since the cyano function allowed an efficient reaction control by IR spectroscopy, we first attempted to attach 1-diethoxymethylindole-5-carbonitrile **2a** [9] to the resin bound diol **3** which we obtained from *Merrifield* resin by coupling with the sodium salt of 2,2-dimethyl-1,3-dioxolane-4-methanol and subsequent acidic hydrolysis according to the literature.[8] Transacetalization under mild acidic conditions should give the resin bound indole **4a** including a five membered ring cyclic acetal. Using 1,4-dioxane as solvent the reaction was performed at room temperature in the presence of catalytic amounts of p-toluenesulfonic acid. Successful formation of the polymer-bound compound **4a** [10] was monitored by FTIR of the carefully washed resin beds when **4a** exhibited a characteristic CN absorption at 2220 cm^{-1}. To demonstrate the reversibility of the process, hydrolysis of the acetal linkage was accomplished using a 1:1 mixture of dioxane and hydrochloric acid. Subsequent treatment with NaOH furnished pure indole-5-carbonitrile (**1a**). Completeness of the cleavage process was also observed by FTIR spectroscopy, showing the virtual disappearance of the CN absorption band. The loading level of resin **4a** was determined to be 0.72 mmol/g based on recovered indole-5-carbonitrile (**1a**). In order to evaluate the scope and limitations of our traceless linking strategy, we next examined the immobilization of DEM protected indoles **2b-e**, using the conditions described above. Results are summarized in Table 1. As can be seen, acceptor substituted indoles **2b,d,e** cleanly couple to the glycerol resin **3**, whereas attachment of 1-diethoxymethylindol (**2c**) failed. The loading capacities of resins **2a-f** were determined after hydrolytic cleavage and recovery of the starting material and were found to be up to 0.76 mmol/g

(82 % of the theoretical). It is worthy to note that not only 3- or 5-substituted indoles were attached to resin 3 but also the sterically more demanding and hydrolytically sensitive 2-tributylstannyl derivatives 2e.

eq 2

Table 1: Immobilization of Indoles

To demonstrate the utility of polymer-bound indoles of type 4 we tried to work out model reactions for the functionalization of the indole nucleus in the positions 2 and 3, respectively. Thus, we planned to subject the polymer-bound stannane **4e** to *Stille* coupling conditions. A *Mannich* reaction starting from resin **4a** was chosen as a typical transformation in position 3. In order to avoid acidic aqueous conditions, **4a** was transformed into the gramine derivative **5** by treatment with dimethylmethyleneimmonium chloride (*Böhme's* salt) [11] in DMF at room temperature. Hydrolysis of **5** afforded 3-dimethylaminomethylindole-5-carbonitrile (**6**) [12] in nearly quantitative yield and excellent purity (>98%) which was determined by careful NMR analysis.

eq 3

Finally, we turned our attention to the resin bound organo tin compound **4e** which should be investigated for its ability to undergo palladium catalized *Stille* cross-coupling [13] employing 4-bromobenzonitrile as a typical electrophile. In fact, the synthesis of the biaryl derivative **7a** succeeded when we used the very recently reported combination of $[Pd_2(dba)_3]$ / t-Bu_3P / CsF as a powerful catalytic system.[14] After hydrolytic cleavage, the 2-phenylindole **7b** was formed in 66 % yield besides 33 % of the indole carboxylate **1b**.

eq 4

In summary, we have developed a novel traceless solid phase linkage using the indole nitrogen as an attachment point. Employing *Mannich* and *Stille* reactions as typical and flexible examples for the functionalization of indoles in the positions 3 and 2, respectively, the

practical utility of this strategy was demonstrated. Applications of this strategy for the solid phase supported synthesis of indole based selective dopamine D4 receptor antagonists as a part of our drug discovery program [15] will be reported in due course.

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(9) Experimental details for the preparation of the DEM protected indole **2a**: A solution of **1a** (889 mg, 6.3 mmol) in triethyl orthoformate (10 ml, 63 mmol) was stirred at 160°C for 24 h. The mixture was concentrated and the residue was purified by flash chromatography (230-400 mesh silica gel, petroleum ether / EtOAc 4:1) to give **2a** (1.390 g, 91 %).

(10) Experimental details for the preparation of the resin bound indole **4a**: A mixture of **2a** (610 mg, 2.5 mmol), resin **3** (550 mg) and p-toluenesulfonic acid (100 mg) in 1,4-dioxane (5 ml) was stirred at room temperature for 3 h, filtered, subsequently washed with 1,4-dioxane, H_2O/EtOH, EtOH and Et_2O and dried in vacuo to give 598 mg of resin **4a**.

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(12) Experimental details for the solid phase supported preparation of the indole **6** including analytical data: Resin **4a** (196 mg, 0.72

6

mmol/g) was suspended in DMF (5ml), treated with dimethyl methyleneimmonium chloride (168 mg, 1.8 mmol) and stirred for 48 h at room temperature. The resin was filtered off and washed with EtOH/H_2O, EtOH and Et_2O to give 150 mg of resin 5. For hydrolysis, resin 5 (150 mg) was suspended in a 1:1 mixture of 1,4-dioxane / 2N HCl (10 ml) and stirred at 40°C for 3 h, followed by addition of 2N NaOH (10 ml) and stirring at room temperature for 0.5 h. The resin was filtered off and washed with EtOAc. The organic layer was dried (Na_2SO_4) and evaporated to give 6 (21 mg) in analytically pure form. ^1H NMR ($CDCl_3$, 360 MHz): d (ppm) = 2.28 (s, 6H, $N(CH_3)_2$), 3.61 (s, 2H, $ArCH_2$), 7.21 (s, 1H, H-2), 7.33-7.40 (m, 2H, H-6, H-7), 8.07 (s, 1H, H-4), 9.05 (br-s, 1H, NH).

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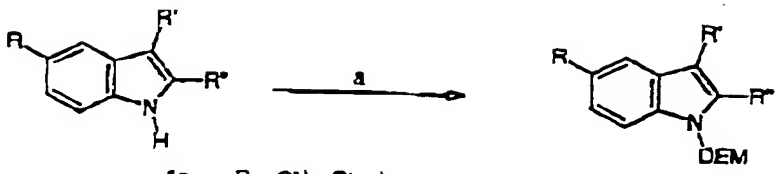


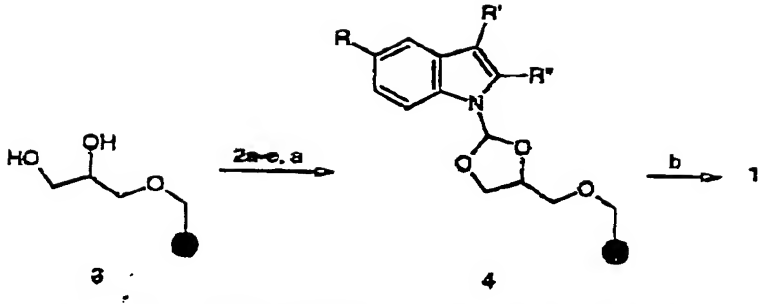
1a	R = CN;	R' = H;	R" = H	2a
1b	R = NO_2;	R' = H;	R" = H	2b
1c	R = H;	R' = H;	R" = H	2c
1d	R = H;	R' = CO_2Me;	R" = H	2d
	R = H;	R' = CO_2Me;	R" = $SnBu_3$	2e

b

a: $HC(OEt)_3$, 160°C, 2-48 h (48-92%); b: 1. n-BuLi / THF, -78°C to 0°C, 0.5 h
2. $ClSnBu_3$, -78°C, 0.5 h (92 %)

092

8



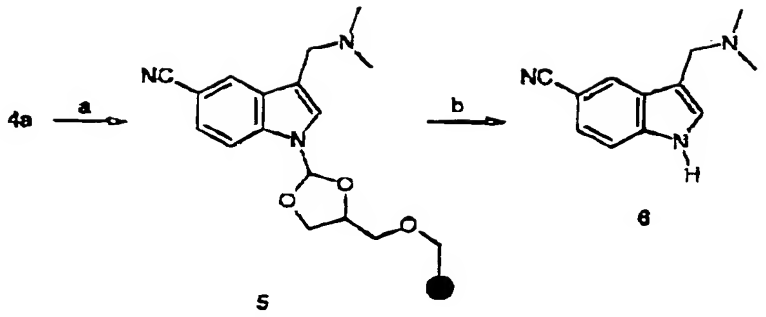
a:1,4-dioxane, TosOH, RT, 3h; b: 1. 1,4-dioxane / 2N HCl, 40°C, 3h;
2. 2N NaOH, RT, 0.5 h

Tab. 1

DHM Protected Indole	R	R'	R"	Resin Bound Indole	Loading (mmol/g)	Cleavage product
2a	CN	H	H	4a	0.72	1a
2b	NO_2	H	H	4b	0.76	1b
2c	H	H	H	4c	—	—
2d	H	CO_2Me	H	4d	0.76	1d
2f	H	CO_2Me	$SnBu_3$	4f	0.42	1d

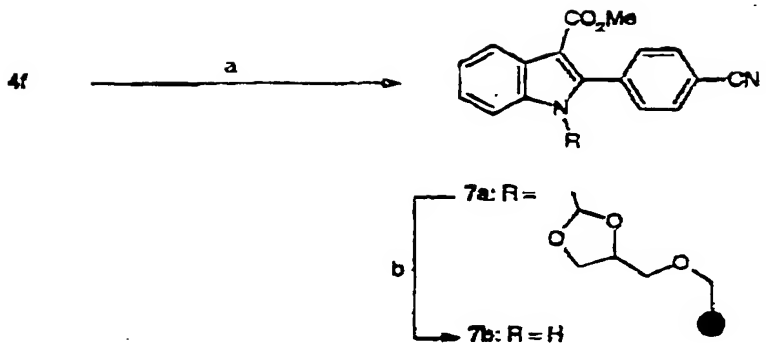
e93

10



a: $[(CH_3)_2NCH_2]Cl$ (10 eq), DMF, RT, 48 h; b: 1. 1,4-dioxane, 2N HCl (1:1), 40°C, 3 h 2. 2N NaOH, RT, 0.5 h (yield: 98 %, purity: 98%)

e94



a: 4-bromobenzonitrile, Pd_2dba_3, t-Bu_3P, CsF, 1,4-dioxane, 100°C, 48 h;
b: 1. 1,4-dioxane, 2N HCl (1:1), 50°C, 3 h 2. 2N NaOH, RT, 0.5 h (66 %).